EXHIBIT D

Systemic Lupus Erythematosus: Demographics, Prognosis, and Outcome

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ABSTRACT. Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder with an annual incidence of 50 to 70/million and a prevalence of 500/million population. The highest incidence is observed in women aged 20 to 40 years. The clinical manifestations of SLE are remarkably heterogeneous. Major organ system involvement may occur in the heart, lungs, kidneys, and central nervous system and is responsible for most of the mortality and morbidity caused by the disease. Complications of drug treatment, in particular corticosteroid side effects, contribute to longterm morbidity. The major causes of death are directly related to the disease and include acute vascular neurologic events, renal failure, cardiovascular or pulmonary involvement, infection, and coronary artery disease. (*J Rheumatol 1997;*(suppl 48)24:67–71)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS PROGNOSIS DEMOGRAPHICS

Systemic lupus erythematosus (SLE) is the most common of the systemic autoimmune disorders[1-3]. Epidemiology of the disease is influenced by age, sex, race, and socioeconomic factors. The annual incidence is estimated to be 50 to 70/million with a prevalence of approximately 500/million. Although lupus may develop at any age, the highest incidence is observed in the age group 20 to 40 years. Females, particularly during the reproductive years, are at significantly greater risk than males with a female to male sex ratio of about 9:1. Racial factors appear to be important with increases in frequency and severity of disease particularly observed in African Americans, Native Americans, Latin Americans, and Chinese.

CLINICAL PHENOTYPES AND DISEASE COURSE

Clinically, SLE is an extraordinarily heterogeneous disease. Most patients present with a clinical illness with constitutional signs (fever, fatigue, weight loss etc.), photosensitivity, rashes, arthritis, and serositis. In many patients the disease course is characterized by similar intermittent flares of the disease, occasionally with minor abnormalities indicative of internal organ involvement. The flares are readily and completely responsive to treatment and diminish in frequency and intensity over time with many patients eventually achieving a state of remission. Complications of drug treatment, in particular corticosteroid side effects, account for much of the longterm morbidity. Involvement of major organ systems may occur in the heart, lungs, kidneys, or central nervous system (CNS) (Table 1). These are responsible for most of the mortality and morbidity including presentations with an acute fulminate, life threatening illness or a chronic, progressive loss of organ function. Fortunately, most forms of major organ involvement in SLE are rare, with the notable exceptions of neurologic and renal disease.

Neuropsychiatric features. Both neurologic and psychiatric manifestations are prominent features of SLE[4]. The epidemiology, natural history, and pathogenesis of neurologic disease in SLE remains very poorly understood. Distur-

Table 1. Major organ involvement in SLE.

Renal
Mesangial, focal, and diffuse proliferative glomerulonephritis
Membranous nephropathy
Glomerulosclerosis
Tubulointerstitial nephritis
Neurologic/psychiatric
Diffuse neurologic syndromes (organic brain syndromes, psychosis, affective disorders, meningitis)
Focal neurologic syndromes (seizures, cerebrovascular events, transverse myelitis)
Movement disorders (chorea, cerebellar ataxia, Parkinson-like)
Peripheral neuropathy (symmetric sensorimotor, mononeuritis multiplex, Guillain-Barré)
Pulmonary
Parenchymal disorders (pneumonitis, alveolar hemorrhage, bronchiolitis obliterans)
Vascular (pulmonary hypertension, pulmonary embolism)
Shrinking lung syndrome
Cardiac
Myocarditis
Endocarditis
Coronary vasculitis
Gastrointestinal
Mesenteric vasculitis
Inflammatory bowel disease
Pancreatitis
Bone Marrow
Aplastic anemia
Hemolytic anemia
Thrombocytopenia
Thrombotic thrombocytopenic purpura

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bances of mental function are most common and range from mild confusion, with memory deficits and impairments of orientation and perception, to frank psychiatric disturbances of hypomania, delirium, and schizophrenia. Seizures are usually of the grand mal type, although petit mal, focal, and temporal lobe epilepsy have been described. Severe headaches, often with scotomata typical of the fortification spectra of migraine are increased. Strokes from hemorrhage or cerebral infarction are seen particularly in patients with antiphospholipid antibodies. Less common neurologic disturbances include cranial neuropathies, transverse myelopathy, aseptic meningitis, pseudotumor cerebri, chorea, hemiballismus, a parkinsonian picture, and both sensory and motor peripheral neuropathies.

Lupus nephritis. In most large series, one-third to one-half of SLE patients have evidence of clinical nephritis. Nephritis typically develops early in the course of lupus with a high proportion of patients who will eventually develop nephritis showing signs of renal involvement at the initial presentation. Loss of renal function occurs very gradually over the course of several years, or more, typically in association with fibrosis and scarring of the kidneys. Clinical courses consistent with rapidly progressive glomerulonephritis are distinctly unusual.

The risk of developing clinical nephritis diminishes with time and the overwhelming majority of clinically relevant lupus nephritis will have appeared during the first 5 years after diagnosis. The onset of nephritis late in the course of the disease is considered to be distinctly unusual. The incidence and severity of nephritis decreases with the age of lupus onset. The differences are most clearly evident at the ends of the age spectrum with 80 to 90% of childhood onset lupus complicated by nephritis[5] as compared to its virtual absence in older populations. The explanation for the influence of age on nephritis is unclear, but presumably involves changes in immune function associated with aging.

Several different forms of renal pathology are recognized and are characterized by inflammation, cellular proliferation of mesangial, endothelial, and epithelial cells, and basement membrane thickening. Late in the process sclerosis of the glomerulus or fibrosis of tubulointerstitial tissues may be seen. There is no clear explanation for the differences in renal pathology observed in SLE nor of the factors responsible for disease progression. It is speculated that physical properties of deposited antibodies or immune complexes, dynamics of tissue deposition and clearance, intrarenal cytokines or genetically determined differences in host reactivity are likely important.

Renal biopsy provides valuable information to assess the prognosis of the renal course. Biopsy findings of mesangial or focal proliferative nephritis are generally associated with a relatively benign disease course, whereas diffuse proliferative or membranoproliferative nephritis indicates a much less favorable renal outcome. The prognosis of membranous nephropathy is far less certain. The biopsy finding of chronic features such as glomerular sclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy predicts a poor outcome[6,7]. In addition, elevated creatinine, hypertension, anemia, hypocomplementemia, young age, and black race are all considered to be discriminators in identifying a subset of patients at increased risk for progressive nephritis.

TREATMENT

Drug therapies for SLE have mainly emphasized the importance of reducing end organ inflammation and the suppression of immune function. The majority of patients with SLE are successfully managed with nonsteroidal antiinflammatory agents, antimalarials, and low dose corticosteroids. Drug regimens are increased in response to flares and gradually tapered during periods of remission. High dose corticosteroids and immunosuppressive drugs are reserved for patients with life threatening manifestations including severe lupus nephritis, central nervous system disease, cardiopulmonary events, or hematologic complications such as thrombocytopenia. Intravenous bolus cyclophosphamide, in particular, has come to assume an important role in the treatment of most serious clinical manifestations, in particular nephritis[8] and CNS disease[9].

There is increasing recognition of the need to develop better approaches to the therapy of SLE. The principal therapeutic needs in SLE are several: (1) The prevention of corticosteroid dependency. In many patients attempts to reduce the dose result in disease exacerbations that require longterm corticosteroid therapy. (2) Prevention of drug toxicities. Complications of drug treatment account for much of the morbidity that develops in SLE, in particular complications of high dose or chronic corticosteroids (infection, osteonecrosis, osteoporosis, coronary artery disease) and cyclophosphamide (infection, sterility, bladder toxicity, malignancy). (3) Treatment failure. Many patients show evidence of continued low grade lupus activity despite optimal treatment and some patients with major organ involvement are resistant to all forms of current therapy.

Other approaches using immunosuppressive drugs are under study. Combined plasmapheresis and cyclophosphamide have been reported to induce longterm clinical remission[10] and an international cooperative trial is currently assessing the regimen in severe renal, CNS, cardiopulmonary, hematologic, and/or leukocytoclastic vasculitis associated with lupus[11]. Cyclosporin A has been reported to be beneficial in lupus membranous nephropathy with substantial reductions in proteinuria and resolution of nephrotic syndrome[12]. Followup renal biopsies suggested reduced deposition of new complexes. Interestingly, no apparent effects on anti-DNA antibodies or complement levels were seen. Improvements in non-major organ lupus with low dose cyclosporin A have been observed in a separate study[13]. Toxicities were minimal and neither study found evidence

of renal toxicities. Although weekly low dose methotrexate is emerging as an important therapy of various forms of systemic vasculitis, clinical studies in SLE have mostly emphasized its role in arthritis, serositis, particularly as steroid sparing agent[14]. Studies of the role of methotrexate in major organ involvement are limited[15]. Preliminary clinical studies suggest a possible role for adenine analogs such as 2-chlorodeoxadenosine or fludarabine in SLE[16].

In murine models of autoimmunity alterations of sex hormones markedly influence autoantibody formation and disease course. Recent clinical studies in SLE patients have demonstrated modest clinical effects with the inhibition of prolactin secretion[17], analogs of gonadotropin releasing hormone[18] and the androgen dehydroepiandrosterone[19].

A number of strategies are in the early phases of clinical development and would appear to be highly promising as potential future therapeutic approaches to the disease. In murine models of autoimmunity, interference with receptors involved in antigen processing has profoundly influenced the development and subsequent course of autoimmunity. The T cell antigen CTLA-4 linked to murine Ig Gγ 2a (CTLA4Ig) has been shown to block autoantibody production and prolong life span in NZB/NZW F_1 mice[20]. Similarly, antibodies to the T cell antigen gp39 (CD40 ligand) have been shown to inhibit autoantibody production and prevent the spontaneous development of nephritis in NZB/NZW[21]. In MRL/*lpr/lpr* mice intramuscular injections of cDNA plasmids encoding for transforming growth factor-ß (TGF-ß) have been shown to increase serum levels of TGF-ß, decrease immunoglobulin production, decrease renal inflammation, and improve survival[23]. Findings included increased serum levels of TGF-ß, decreased immunoglobulin production, decreased renal inflammation, and improved survival. An antibody cloned from MRL/*lpr/lpr* mice which shares an idiotype present in SLE serum has been used as a vaccine and appears to be capable of generating an antiidiotype response[23]. Finally, murine and human studies of a synthetic double stranded oligodeoxynucleotide linked through a nonimmunogenic platform (LPJ 394) have been shown to reduce levels of anti-DNA antibodies[24] presumably as a consequence of the induction of B cell tolerance to nucleoprotein antigens.

PROGNOSIS AND OUTCOME

Most studies assessing prognosis have been done in patients with lupus nephritis in which both clinical, demographic, and renal biopsy findings have been found to be predictive of the course of renal disease[25]. Many studies have attempted to correlate specific autoantibodies with SLE clinical manifestation. Although weak correlations have been detected (Table 2), none has been sufficiently convincing to be useful at a clinical level, particularly in predicting organ involvement. Antibodies to dsDNA generally are regarded as a marker antibody for lupus nephritis. However, discordance between antibodies to DNA, and other serologic abnormalities, and clinical lupus activity is not uncommon[26]. It has been proposed that only highly charged cationic antibodies to DNA are associated with nephritis[27]; however, assays to specifically measure and quantitate cationic DNA antibodies are not routinely available. Recently a c-DNA clone encoding cationic anti-DNA antibodies associated with severe lupus nephritis has been isolated[28]. The antibody appears to be derived from a novel germ line gene conferring a cationic charge with somatic mutations inducing affinity maturation of the antibody. These findings are of considerable interest with the potential to improve our understanding of both the genetic and antigenic components that contribute to lupus nephritis.

Table 2. Association of autoantibodies with clinical findings in SLE.

Autoantibody	Clinical Association
dsDNA	Nephritis
Sm	? Nephritis ? CNS
Ribosomal P	Psychosis, hepatitis
Cardiolipin	Thrombosis, thrombocytopenia, fetal loss
SSA, SSB	Subacute cutaneous lupus, neonatal lupus syndrome, Sjögren's
U1-RNP	Mixed connective tissue disease

A negative association between rheumatoid factor and lupus nephritis has been documented in several studies[29]. It has been hypothesized that the binding of rheumatoid factor to the immune complexes that form in lupus both enhances clearance of the complexes by the reticuloendothelial system and interferes with deposition of the complexes along endothelial surfaces. There have been limited studies as to the influence of other autoantibodies on lupus nephritis. McCarty and colleagues have described a distinctive autoantibody profile of antibodies to Ro/SSA, nuclear RNP, and Sm in black female patients with nephritis[30].

There has been considerable research interest in the possibility that genetic markers are involved in specific organ involvement, particularly severe nephritis. Studies of

Table 3. Survival in SLE.

Adults	Percentage Surviving 5 Year	10 Year	15 Year
Pistner, *et al* (Los Angeles)[34]	97	93	83
Ward, *et al* (Durham)[35]	82	71	63
Abu-Shakra, *et al* (Toronto)[36]	93	85	79
Massardo, *et al* (Chile)[37]	92	77	66
Children			
Plart, *et al* (Minneapolis)[38]	85	85	72
Glidden, *et al* (Boston)[39]	92	85	72
Levy, *et al* (France)[40]	92	88	84
Cameron (London)[41]	88	85	77

murine models of SLE suggest that there is no single gene responsible for nephritis, but rather multiple different genes are involved that operate in a threshold manner[31]. Genetic studies in patients have revealed modest associations between Class II histocompatibility alleles[32] and with FcγRIIA alleles in African-Americans[33].

Clinical studies reporting overall survival of adults[34–37] and children[38–41] with SLE have yielded data that are in reasonable agreement as to mortality over the first decade of illness (Table 3). The major causes of death are from clinical manifestations directly related to lupus *per se* including acute vascular neurologic events, renal failure, and cardiovascular or pulmonary involvement, infection[42], and coronary artery disease[43]. Subset analysis of survival of patients with poor prognosis SLE and selection criteria for autologous stem cell transplantation are detailed elsewhere in these proceedings[44].

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